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Dated: November 21, 2008 /Sharon M. Sintich Reg. No. 48,484/
Electronic Signature for Sharon M. Sintich:
:

Docket No.: 9189
(01017/40451B)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,790 Art Unit: 1646

Filed: May 19, 1995 Examiner: Z. Howard

For: HUMAN TNF RECEPTOR

RENEWED PETITION UNDER 37 C.F.R. §1.181(F)

REQUESTING FURTHER REVIEW AT A HIGHER LEVEL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby petition the Director under 37 C.F.R. §1.181 (and, to the extent necessary, under 37 C.F.R. §§ 1.182 and 1.183) for review at a higher level of the Technology Center (TC) Director's denial-in-part of Applicant's petition to correct the Examiner's failure to identify new grounds of rejection in the Examiner's Answer mailed August 14, 2008. This petition is timely filed within two months of the September 23, 2008 mailing date of the TC Director's Decision on Petition. See 37 C.F.R. §1.181(f).

I. Statement of the Facts Involved

A. The Presently Pending Claims

The claims in the present application relate generally to fusion proteins comprising (a) a TNF-binding soluble fragment of a human TNF receptor (TNFR) having a molecular weight of about 75 kD, and (b) all of the domains of the constant region of a

human immunoglobulin heavy chain other than the first domain of said constant region. The TNFR of about 75 kD is also referred to as the "p75 TNFR."

B. Relevant Prosecution History

As discussed below, Appellants' evidence of unexpected results, submitted in January 12, 2005 and in October 3, 2006, was never considered in detail until the Examiner's Answer mailed August 14, 2008, *more than three years after* the first submission. The Examiner's Answer, while admitting the unexpected nature of most of the results, asserted *for the first time* that the number of species for which unexpected results were shown did not "extend to the full range" of Appellants' claims. As discussed in section III below, the assertion of this new rationale for rejection for the first time in the Examiner's Answer deprived Appellants of the opportunity to rebut this basis for rejection by, for example, amending the claims or submitting appropriate evidence.

On July 12, 2004, a non-final Office Action was issued which rejected the claims under 35 U.S.C. § 101 and 102(e). In a response dated January 12, 2005, Appellants amended the claims to address the rejections. Although an obviousness rejection was not pending, in an effort to expedite prosecution Appellants provided data showing the unexpected binding activity and TNF-neutralization activity of three different species of TNF fusion proteins within the scope of the then-pending claims: p55 TNFR/IgG3 fusion proteins, p75 TNFR/IgG3 fusion proteins and p75 TNFR/IgG1 fusion proteins.

The subsequent office action mailed April 5, 2005 did not reject the claims under 35 U.S.C. §103. That office action also explicitly stated that at least some of the evidence of unexpected results was considered (the two declarations of Dr. Werner Lesslauer under 37 C.F.R. §1.132 relating to p55 TNFR/IgG3 and p75 TNFR/IgG3 fusion proteins), and *did not identify any insufficiency in Appellants' evidence of unexpected results.* (Office Action dated April 5, 2005, p. 2). Appellants' response mailed October 5, 2005 amended the claims to be directed to the p75 TNFR fusion proteins. Subsequently, a different Examiner was assigned to the case.

On April 3, 2006, a non-final Office Action was issued that rejected the claims as lacking written description. The Office Action also newly rejected the claims as obvious over two references, Dembic *et al.* (Cytokine 2:231-237, 1990) and Capon (U.S. Patent 5,116,964). The Dembic reference discloses p75 TNFR sequence. The Capon reference was cited for its general disclosure of fusion proteins comprising immunoglobulin fragments.

On June 22, 2006, the Examiner, his supervisor, and another primary examiner granted an interview to Appellants' attorneys and inventor Dr. Werner Lesslauer. As noted in Appellants' subsequent response mailed October 3, 2006, "[d]uring the interview, Applicants discussed and *the Examiners agreed to consider data* showing a number of unexpected results associated with the claimed TNF-binding fusion proteins." [Emphasis added.] (October 3, 2006 response, p. 17.)

As part of their response mailed October 3, 2006, Appellants discussed the data presented in the previous response dated January 12, 2005 and submitted additional evidence of unexpected results. Exhibits A-C of the response of January 12, 2005 contain data demonstrating improved binding kinetics and potency in *in vitro* assays of biological activity . Exhibits C, L, Q, and R of the response of October 3, 2006 contain data demonstrating an unexpected lack of aggregation ability and reduced immunoglobulin effector functions for a p75 TNFR/IgG1 fusion protein. Thus, Appellants' June 22, 2006 interview and October 3, 2006 response argued the relevance of a variety of different data for two different species of fusion proteins within the scope of the claims: extracellular domain of p75 fused to the hinge of IgG1 and extracellular domain of p75 TNFR fused to the hinge of IgG3. Excerpts from the October 3, 2006 response reproduced below show that Appellants argued based on these unexpected results that the claims were unobvious.

> Thus, against the expectation in the art as of the application's effective filing date that dimeric TNFR fusion proteins would bind two ligands and form aggregates, the observed binding stoichiometry and lack of ability to aggregate is an unexpected advantageous property that renders the claimed TNF-binding fusion protein nonobvious. [October 3, 2006 response, p. 21.]

> Thus, against the expectation in the art as of the application's effective filing date that the claimed TNFR fusion proteins would bind to FcγR or C1q and retain pro-inflammatory immunoglobulin effector functions, the observations that a fusion of soluble p75 TNFR to the hinge region of IgG ***lacks*** ability to bind FcγR or C1q and exhibits ***markedly*** decreased ADCC and CDC effects are quite surprising unexpected and advantageous results that show that the claimed invention was unobvious. [October 3, 2006 response, p. 24, emphasis in original.]

> . . . . the observed increased binding affinity, increased kinetic stability, and 1000-fold increase in *in vitro* biological activity are unexpected and advantageous results that show that the claim invention was unobvious. [October 3, 2006 response, p. 26.]

On February 23, 2007, a final office action ("Final Action") was issued which maintained the written description rejections, albeit with a newly stated position and rationale. The obviousness rejection was also maintained over the same references, Dembic and Capon. Appellants' evidence of unexpected results *was considered insufficient* ***solely*** *on the ground that the results were generated using a species that was asserted to be inadequately described.* The only portion of the Office Action which addressed Appellants' evidence is reproduced below in its entirety:

> Applicants further argue that the 103 rejection should be withdrawn in view of a number of unexpected results associated with the claimed TNF-binding fusion proteins. Applicants present data supporting three categories of unexpected results: lack of aggregation ability; markedly reduced immunoglobulin effector function; and "binding affinity, kinetic stability and potency".
>
> Applicants' arguments have been fully considered but are not found persuasive. The evidence of unexpected results presented by Applicants is not sufficient to overcome the rejection. Applicants' putative unexpected results appear to be generated using a fusion protein comprising the full-length extracellular domain of the insoluble 75 kD TNF binding receptor and portions of an immunoglobulin molecule. However, as set forth above, in the section "Claim Rejections – 35 U.S.C. 112, 1st paragraph, written description", **the specification does not provide a description of this particular species of fusion protein. There is no conception in the specification at the time of filing of this particular species of fusion protein. Therefore, the evidence of unexpected results found with this particular species of receptor-Ig fusion is not sufficient** to overcome the obviousness of combining the teachings of Dembic in view of Capon. [Pages 18-19 of Final Action; emphasis added.]

On August 2, 2007, Appellants submitted a response with declaratory evidence addressing the new position on written description set forth in the Final Action. Appellants reiterated their disagreement with the obviousness rejection.

On October 9, 2007, an advisory office action ("Advisory Action") was issued. The Advisory Action contained no additional discussion with respect to the obviousness rejection. Appellants' declaratory evidence regarding written description was admitted into the record, although this evidence was not considered sufficient to overcome the written description rejections. Appellants appealed and filed their appeal brief on February 25, 2008.

In the Examiner's Answer mailed on August 14, 2008, Appellants' evidence regarding unexpected results was substantively considered in detail for the first time. The Examiner's Answer discussed each type of result and whether the Examiner agreed that it was unexpected. For example, the Examiner conceded that the drastically reduced effector function (pages 64-65), the failure to form aggregating complexes (page 65), the increase in TNF neutralizing potency (page 66), the increased kinetic stability (page 67) and the improved inhibition of TNF (page 67) were each unexpected results. *None of this detailed discussion that appears in the Examiner's Answer was present in the Final Action*, despite Appellants' ten pages of discussion of their unexpected results in the prior filed response, including explicit arguments that these unexpected results were sufficient to rebut the obviousness rejections (pp. 17-26 of response mailed October 3, 2006).

Furthermore, the Examiner's Answer newly stated that "Appellants do not provide any evidence that the unexpected results *extend to the full range* of the claimed genus of 'soluble fragments' of part (a) of each claim, including mutated variants of a 75 kD insoluble TNF receptor." (Examiner's Answer, p.64; emphasis added). The Answer acknowledged that unexpected results sufficient to rebut obviousness could consist of unexpected results for a single member of a claimed subgenus or for a narrow portion of a claimed range. (Examiner's Answer, p. 63). However, the Examiner's Answer newly alleged that "the skilled artisan could not ascertain a trend in the exemplified data that would allow

him to *reasonably extend the probative value thereof.*" (Examiner's Answer, p.64; emphasis added).

The Examiner's Answer also included novel factual assertions and new rationales for rejection that were deemed by the TC Director's Decision on Petition to be improper new grounds of rejection that were not identified as such. Appellants do not appeal the portion of the TC Director's Decision that granted-in-part Appellants' request for relief.

II. Relief Requested

The Examiner's Answer has been vacated by the TC Director's Decision on Petition dated September 23, 2008 which granted-in-part Appellants' request for relief. However, that Decision denied-in-part Appellants' request for relief with respect to the newly raised issue of whether the number or probative value of the unexpected results "extends to the full range" of the claims.

Upon review at a higher level, the Director is requested to reverse that aspect of the TC Director's Decision and render a new decision directing the Examiner to provide a corrected Examiner's Answer that properly identifies the new ground of rejection and includes the approval of the TC Director or designee.

III. Statement of Reasons That Requested Relief Should Be Granted

Any new ground of rejection made by an examiner in an answer must be prominently identified as a new ground of rejection. MPEP §§ 1207.02 and 1207.03. The test for "whether a rejection is considered 'new' in a decision by the board [or in an examiner's answer] is whether appellants have had fair opportunity to react to the thrust of the rejection". *In re Kumar*, 418 F. 3d 1361, 1368, 76 U.S.P.Q.2d 1048 (Fed. Cir. 2005), citing *In re Kronig*, 539 F. 2d 1300, 1302, 190 U.S.P.Q. 425 (CCPA 1976). "Where the board makes a decision [or an examiner makes a rejection] advancing a position or rationale new to the proceedings, an applicant must be afforded an opportunity to respond to that position or rationale by submission of contradicting evidence." *In re DeBlauwe*, 736 F. 2d

699, 706 n.9, 222 U.S.P.Q. 191 (Fed. Cir. 1984) citing *In re Eynde* 480 F.2d 1364, 1370, 178 U.S.P.Q. 470 (CCPA 1973).

A. New Ground of Rejection Relating to Sufficiency of Unexpected Results

As explained above in section I.B., Appellants first provided evidence of unexpected results, with respect to two different species within the scope of Appellants' claims, on January 12, 2005. Over the subsequent *three years*, the Patent Office had at least four opportunities to question the sufficiency of the number of species for which unexpected results were shown, or the "probative value" of such results, in the office actions of April 5, 2005, April 3, 2006 and February 23, 2007, and during the in-person interview of June 22, 2006. However, that position and those rationales were advanced *for the first time* ***after appeal,*** at a time when Appellants no longer had the right to provide new evidence or data. The failure to provide notice to Appellants of the Patent Office's position deprived Appellants of a fair opportunity to respond. Therefore, these objections to the Appellants' unexpected results, provided for the first time in the Examiner's Answer, constitute a new ground of rejection and are manifestly untimely at this stage after appeal.

The Examiner has an obligation to advance prosecution before appeal. Under MPEP § 706.07,

> Before final rejection is in order a clear issue should be developed between the examiner and applicant. . . . The examiner should never lose sight of the fact that in every case the ***applicant is entitled to a full and fair hearing***, and that a clear issue between applicant and examiner should be developed, if possible, ***before appeal***. [Emphasis added.]

Moreover, when Appellants submit evidence to support nonobviousness of the claimed invention, the Examiner has an obligation to *identify the reasons* and explain *specifically* why the evidence is insufficient:

> Where the evidence is insufficient to overcome the rejection, the examiner must ***specifically explain why the evidence is insufficient***. General statements such as "the declaration lacks technical validity" or "the evidence is not commensurate with

> the scope of the claims" without an explanation supporting such findings are insufficient. [MPEP §716.01; emphasis added.]
>
> If, after evaluating the evidence, the examiner is still not convinced that the claimed invention is patentable, the next Office action should include a statement to that effect and ***identify the reason(s)*** (e.g., evidence of commercial success not convincing, the commercial success not related to the technology, etc.). [MPEP §716.01(d); emphasis added.]

The first and only time the Examiner commented on the sufficiency of the evidence of unexpected results was in the Final Action, dated February 23, 2007. See pp. 18-19 of the Final Action; quoted in its entirety above in Section I.B. The *only* reason identified for the alleged insufficiency of the unexpected results was the alleged lack of written description or "conception" of the particular species of fusion protein used in the experiments. The Final Action did not question the sufficiency of the *number of different* species for which unexpected results were shown as not "*extend[ing] to the full range*" of the claims, as stated in the Examiner's Answer. The Final Action did not indicate that unexpected results should be shown for fusion proteins comprising *mutated variants* of p75 TNFR, as stated in the Examiner's Answer. The Final Action did not allege that the skilled artisan would not "*reasonably extend the probative value*" of the results to the full range of the claimed genus, as stated in the Examiner's Answer. The Advisory Action, dated October 10, 2007, provided no additional comments regarding the obviousness rejection under 35 U.S.C. § 103.

Appellants thus were led to believe that the sole issue with respect to the insufficiency of unexpected results was the asserted lack of literal written description of the species for which unexpected results were shown. If there were *other* reasons for deeming the evidence insufficient, the Patent Office should have identified them earlier, for example, in the office actions of April 5, 2005, April 3, 2006 and February 23, 2007, or during the in-person interview of June 22, 2006. As noted above, a general statement that evidence is insufficient is inadequate; instead, a specific explanation of the reasons is required. See, *e.g.*, MPEP §716.01.

In this case, Appellants had submitted evidence with respect to two representative species falling within the scope of the claims: a p75 TNFR/IgG3 fusion protein and p75 TNFR/IgG1 fusion protein. There have been cases in which nonobviousness of a genus of compounds was established based on even a single showing of unexpected results. See, for example, *Application of Papesch*, 315 F.2d 381, 383, 137 U.S.P.Q. (BNA) 43, (CCPA 1963).[1] It was thus essential that the Patent Office provide notice that a specific rationale for the insufficiency of evidence was the insufficiency of the number of different species for which unexpected results were shown.

Although Appellants are grateful for the TC Director's speedy review of the petition, the denial-in-part of Appellants' request for relief was based on factually incorrect findings and is contrary to controlling precedent. The Decision on Petition was incorrect in stating that the "examiner's initial finding [was] that petitioner's unexpected results were not accepted as being commensurate in scope with the breadth of the claimed invention." Decision on Petition, p. 2. The only objection, before appeal, to the sufficiency of evidence was the rationale that the "particular species" for which the results were shown lacked "description" or "conception" in the specification. The words "commensurate" or "scope" do not appear anywhere in regards to the obviousness rejection at pp. 18-19 of the Final Action or the Advisory Action.

It is also incorrect that the novel rationales were "merely supporting the examiner's initial finding" and could be characterized as "statements by the examiner which tend to support or solidify a rejection previously instituted." Decision on Petition, p. 2. The initial rationale set forth in the Final Action, that the evidence was insufficient due to lack of "description" or "conception," is not at all similar to the new rationale in the Examiner's

[1]In Papesch, the appellate court reversed the Board's finding of obviousness in its entirety, with respect to all claims 1-3, based on unexpected results for the single species of claim 2. The court stated: "proof has been given showing that the compound of claim 2, 'a representative member of' the group of compounds claimed, possesses an advantageous pharmacological property shown not to be possessed by the prior art compound. In filing the affidavit, appellant stated in his response to the office action that the compounds of his claims 1 and 3 included more distantly related compounds than the triethyl compound tested and submitted that the showing of unpredictable and 'completely dissimilar biological properties' established the patentability of the compounds he claimed."

Answer that the results do not "extend to the full range" of the claim. There is nothing in that initial rationale that would suggest that the *number* of different species was insufficient.

The fact that the two rationales are wholly different is apparent from considering the different responses to each rationale. An appropriate response to the initial rationale in the Final Action would be to show description or conception of the species in the specification, since that was what was asserted to be lacking. There would be no reason to supply evidence relating to additional species. Similarly, there would be no need to supply an argument as to why the unexpected results had sufficient probative value to extend to the full range of the claim. In contrast, a response to the new rationale in the Examiner's Answer would not include any showing of description or conception of the species in the specification. Instead, such a response might include new evidence with respect to additional species, amendment to the claims, or argument regarding probative value of the evidence extending to the full range of the claim. Thus, it is factually incorrect that the newly asserted rationale merely supports or solidifies the initial finding.

Moreover, the TC Director's opinion that it is permissible to assert new rationales that "merely support[] the examiner's initial finding" is contrary to controlling precedent. The Court of Customs and Patent Appeals (CCPA) addressed this issue in *In re Waymouth*, 486 F. 2d 1058, 179 U.S.P.Q. 627 (CCPA 1973), amended on other grounds after rehearing, 489 F. 2d 1297, 180 U.S.P.Q. 453 (CCPA 1974), stating that:

> To attempt to *deny appellants an opportunity to provide a different and appropriate response* to the board's rejection by saying that the board merely advanced "an additional reason" for affirming the examiner begs the question and *does not satisfy the administrative due process* . . . [*Id.*, 486 F.2d at 1061; emphasis added.]

In *Waymouth*, the examiner rejected the claims as containing new matter because of their recitation of "sodium iodide." On appeal, the board agreed with appellants on the issue of sodium iodide, but instead held that the claims contained new matter because of their recitation of "0.17 mg/cc" of sodium iodide. The board denied the applicant's petition for reconsideration on the ground that its comments concerning the mg/cc limitation

were merely "an additional reason" for affirming the examiner's rejection based on new matter.

In reversing the board, the CCPA explained:

> We believe the prosecution history of this application clearly shows that the examiner was only concerned with an alleged failure to disclose sodium iodide. However, after finding for appellants on this issue, the board proceeded to sustain the rejection on a wholly different basis. Although the same phrase ("sodium iodide ... present in amount of at least 0.17 mg./cc. of arc tube volume") was questioned by both the examiner and the board, the bases of their rejections were wholly different, necessitating different responses by appellants. [*Id.*, 486 F.2d at 1060-61; emphasis added.]

The present situation is parallel to that in *Waymouth*. Although the pre-appeal and post-appeal rejections nominally appears to be that the "evidence of unexpected results presented by Applicants is not sufficient to overcome the rejection," the underlying pre-appeal rationale asserted to explain the insufficiency was wholly different from the post-appeal rationales in the Examiner's Answer. Thus, as in *Waymouth*, denying Appellants in this case any notice of the novel rationales and the opportunity to provide a different and appropriate response violates administrative due process.

Contrary to the opinion of the Decision on Petition, pp. 2-3, the present situation *is* analogous to that in *In re DeBlauwe*, *supra.* In *DeBlauwe*, despite appellants' arguments throughout prosecution that articles with the claimed expansion ratios unexpectedly overcame a longstanding problem, the Board and the Examiner failed to state their position that there was no objective evidence of unexpected results. Because of this lack of notice and opportunity to respond, the Federal Circuit vacated the Board's decision and remanded the case, stating:

> In view of the PTO's failure to challenge the sufficiency of appellants' rebuttal evidence until this appeal, when appellants could no longer offer evidence, we conclude that it is necessary to vacate the board's decision on claims 42-51 and 53 and to remand the case to afford appellants the opportunity to submit objective evidence of unexpected results. *In re DeBlauwe*, 736 F. 2d at 706.

In the Decision on Petition, the TC Director stated that *In Re DeBlauwe* is not relevant to the instant case because the Examiner provided "ample" reasons in the prosecution history with regard to the insufficiency of the unexpected results. As stated above, the Examiner's reasons were provided in only two paragraphs in the Final Action, in response to Appellants ten pages of discussion of the unexpected results, and did not identify the new post-appeal rationales. This can hardly be viewed as "ample."

The thrust of the decision in *DeBlauwe* was that the Patent Office is required to provide notice to appellants of its reasons for challenging the sufficiency of evidence, in order to afford appellants an opportunity to respond. In this case, as in *DeBlauwe*, the PTO's failure to articulate reasons for insufficiency of Appellants' rebuttal evidence until this appeal, when there is no longer an opportunity to offer additional evidence, requires that the new reasons be designated a new ground of rejection so that Appellants are afforded a fair opportunity to respond. Consideration of these new rationales on appeal would be inappropriate because Appellants have not had a fair opportunity to respond, and consequently the record does not adequately address this issue. Moreover, advancing a novel position or rationale on appeal, when new evidence with respect to additional species and amendments cannot be introduced, deprives Appellants of administrative due process.

CONCLUSION

In accordance with the Administrative Procedure Act, the PTO must assure that an applicant's petition is fully and fairly treated at the administrative level, without interim need for judicial intervention. See *Dickinson v. Zurko*, 527 U.S. 150, 154, 144 L. Ed. 2d 143, 119 S. Ct. 1816 (1999) (the PTO is an agency subject to the Administrative Procedure Act). Appellants would be denied administrative due process if the Examiner were permitted to delay substantive consideration of evidence and, after appeal, institute a new rationale for rejection without designating it as a new ground for rejection.

Applicants believe that the requested relief should be granted, for all of the reasons explained above, and respectfully solicit a prompt decision on all issues. This petition is submitted with the requisite fee under 37 C.F.R. 1.17(f). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 13-2855, under Order No. 01017/40451B.

Dated: November 21, 2008

Respectfully submitted,

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